A review of pioglitazone HCL and glimepiride in the treatment of type 2 diabetes

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Abstract: Type 2 diabetes (T2D) is a progressive disorder with a consistent and steady increase in glycosylated hemoglobin (HbA_1c) over time associated with enhanced risk of micro- and macrovascular complications and a substantial reduction in life expectancy. There are three major pathophysiologic abnormalities associated with T2D: impaired insulin secretion, excessive hepatic glucose output, and insulin resistance in skeletal muscle, liver, and adipose tissue. These defects have been treated in clinical praxis by use of oral insulin secretagogues (sulfonylureas/glinides) or insulin, biguanides, and thiazolidinediones (TZDs) respectively. Pioglitazone HCL is an insulin sensitizer in the TZD family and glimepiride is an insulin secretagogue in the SU family. This article reviews mechanisms of action and clinical data behind the use of these two commonly used oral hypoglycemic agents with documented efficacy and good safety profile of once-daily administration, alone or in combination with insulin or metformin, in the management of T2D in terms of glycemic and non-glycemic effects, tolerability and side effects, and impact on vascular health.

Keywords: pioglitazone, glimepiride, type 2 diabetes, thiazolidinediones, sulfonylureas

Search criteria

Studies were obtained from searches of databases MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials, using search terms; type 2 diabetes, pioglitazone, glimepiride, sulfonylureas, and thiazolidinediones limiting for English language. The last search was conducted in March 2007.

Mechanisms of action

Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of peroxisome-proliferator activated receptors γ (PPARγ) (Lehmann et al 1995; Henry 1997), which are nuclear receptors, composed of three major isoforms (α, β/δ, and γ). PPARγ is a transcription factor, when activated by TZDs, promoting transcription of insulin-sensitive genes involved in fatty acid and glucose uptake and lipogenesis and thereby enhance or partially mimic selective actions of insulin (Saltiel and Olefsky 1996). PPARγ is also essential for normal adipocyte differentiation and proliferation (Lemberger et al 1996). PPARγ is expressed in key target tissues for insulin action, most abundantly in adipose tissue but also in skeletal muscle, liver, pancreatic β-cells, vascular endothelium, and macrophages (Dubois et al 2000; Willson et al 2001). The glucose-lowering effect of TZDs is attributed to increased peripheral glucose disposal (Nolan et al 1994; Miyazaki et al 2001a, b; Miyazaki et al 2002a) and decreased hepatic glucose output (Miyazaki et al 2001a). There is also evidence of increased insulin secretory response in subjects with type 2 diabetes (T2D) following treatment with TZDs (Miyazaki et al 2002b; Wallace et al 2004), and a recent in vitro study of acute effects of the PPARγ agonist

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pioglitazone on human islets from subjects both without and with T2D suggests that short-term pretreatment with pioglitazone primes both healthy and diabetic human islets for enhanced glucose-sensitive insulin secretion (Zhang et al 2006). TZDs have been shown to cause redistribution of fat from hepatic and visceral adipose tissue to subcutaneous adipose tissue (Miyazaki et al 2002a; Shadid and Jensen 2003; Rasouli et al 2005; Smith et al 2005), and in this way possibly saving tissues such as liver, skeletal muscle, and pancreatic β-cells from lipotoxicity.

Two TZDs are currently approved for treatment of hyperglycemia in T2D, rosiglitazone and pioglitazone, which are both potent and highly selective agonists for PPARγ, being very similar in mechanism of action, effect on hyperglycemia, and side effect profiles. It is important to keep in mind that these drugs need insulin as a co-factor for PPAR agonism (Feinglos and Bethel 1998), and if used at late stages of T2D, when insulinopenia has already developed, the full effect cannot be expected.

Pioglitazone HCL is a PPARγ agonist that increases both insulin-stimulated glucose uptake in peripheral tissues (Miyazaki et al 2001b) and insulin sensitivity in hepatic and adipose tissue (Kawamori et al 1998; Miyazaki et al 2004), thereby lowering plasma glucose both as single agent and in combination with other oral hypoglycemic agents (OHA) and/or insulin (Aronoff et al 2000; Rosenblatt et al 2001; Scherbaum and Goke 2002; Herz et al 2003). Pioglitazone has also been shown to have multiple beneficial effects on lipid metabolism (Winkler et al 2003; Khan et al 2004; Perez et al 2004; Betteridge and Verges 2005; Goldberg et al 2005), endothelial function (Forst et al 2005b; Martens et al 2005), atherogenesis (Langenfeld et al 2005; Mazzone et al 2006), fibrinolysis (Derosa et al 2005b), and immune function (Marx et al 2000; Gosset et al 2001; Martens et al 2006).

Pioglitazone has in addition shown some minor activation of PPARα (Forman et al 1995; Lehmann et al 1995). This activation has been linked to lowering of plasma triglyceride (TG) levels. PPARα activation is also known to have anti-inflammatory effects and preventive effect on arteriosclerosis (Rubins et al 1999; Duez et al 2002).

Sulfonylureas

Sulfonylureas (SUs) are widely used drugs in the treatment of T2D. They exert their insulin-releasing effect mainly by inhibiting ATP-sensitive potassium channels. In the pancreatic β-cell this action induces depolarization of the cell membrane, allowing an influx of calcium in the cell. This in turn induces insulin release into the blood (Ashcroft and Rorsman 1989). The insulin release is not modified by plasma glucose and the SU action can thus induce hypoglycemia.

It is, however, also evident that SUs have insulin-releasing effects independent of ATP-sensitive potassium channels. Tolbutamide, glibenclamide, and glipizide were shown to increase insulin secretion in human β-cells also when the membrane of the β-cell was voltage-clamped and thus Ca-flux was unaffected (Eliasson et al 1996). It was also suggested that this action was mediated by protein kinase C (PKC), since the stimulatory action of tolbutamide was abolished by a PKC inhibitor. Recent studies of rat β-cells have shown that glibenclamide inhibits activity of carnitine palmitoyltransferase 1 (CPT 1) which in turn switches fatty acid catabolism to synthesis of PKC-activating lipids and CPT 1 may thus play a major role in SU-mediated insulin release (Lehtihet et al 2003). In this context it is also interesting to note that it was shown long ago (Hellman et al 1984) that glibenclamide accumulates in the β-cell during chronic treatment.

ATP-sensitive potassium channels are not specific to the pancreatic β-cell but found in a variety of cells throughout the human organism. These cells include vascular smooth muscle cells (Quayle et al 1997) vascular endothelium, cardiac myocytes (Nichols and Lederer 1991) and some brain neurons (Yamada et al 2001). ATP-sensitive potassium channels are also found on the inner membranes of mitochondria (Dahlem et al 2004). In all mentioned cell types, opening of KATP channels in response to metabolic stress leads to inhibition of electrical activity and are in that way involved in the response of both cardiac and cerebral ischemia. The K channels consist of two entities: Kir6 (belonging to the family of inwardly rectifying K^+ (Kir) channels) and a SU receptor, SUR. There is more than one isoform of both Kir6 (Kir6.1, Kir6.2) and SUR (SUR1, SUR2A, SUR2B) (Proks et al 2002). Kir6 and SUR are associated in different ways in body tissues and show different sensitivity to various K blockers. It is well established that SU can block ATP-sensitive potassium channels also in cells outside the pancreas. It has been proposed that ischemic preconditioning is a mechanism of protection against myocardial ischemia. It has been described as an adaptive response of the myocardium to repeated episodes of ischemia and the proposed mechanism is an opening of ATP-sensitive potassium channels in the mitochondria. The blocking of potassium channels in the heart by SU medication has given rise to a long-standing concern regarding the potential adverse effects of SU medication in

the event of ischemic heart disease. See below for a review of existing data.

Clinical trials

Pioglitazone HCL in treatment of T2D

Effect on plasma glucose, insulin sensitivity and lipids

Pioglitazone 7.5–45 mg daily has been compared with placebo in several randomized, double blind, parallel-group studies in patients with T2D. Pioglitazone 15, 30, and 45 mg produced significant improvements in HbA_{1c} and fasting plasma glucose (FPG). Mean change in HbA_{1c} from baseline ranged from –0.3% to –1.8% and up to –2.6% when adjusted for difference from placebo. Pioglitazone also produced significant decreases in TG and significant increases in high density lipoprotein (HDL) (Aronoff et al 2000; Rosenblatt et al 2001; Scherbaum and Goke 2002; Herz et al 2003).

In comparative/combination trials with metformin, in a 1-year, active-comparator trial, patients poorly controlled with SU were randomly assigned to metformin or pioglitazone. Both treatments resulted in comparable reductions in HbA_{1c} and FPG with sustained glycemic control throughout the study (Hanefeld et al 2004). In a combination trial metformin plus pioglitazone 30 mg was compared with metformin plus placebo in patients with poorly controlled T2D. Treatment with pioglitazone 30 mg plus metformin resulted in significant improvement in HbA_{1c} and FPG compared with placebo plus metformin. In addition, patients treated with metformin plus pioglitazone had a significant reduction in TG and a significant increase in HDL-C compared with metformin plus placebo (Einhorn et al 2000). During two active-comparator trials, treatment with metformin and pioglitazone resulted in equal, significant reduction in HbA_{1c} while insulin sensitivity measured by homeostasis model assessment showed significant improvement in the pioglitazone, but not the metformin group at 32 weeks (Pavo et al 2003; Schernthaner et al 2004b).

In comparative/combination trials with SUs, pioglitazone produced comparable reduction in HbA_{1c} and FPG as SU. Pioglitazone produced a slower but sustained reduction in HbA_{1c} compared with an earlier effect in the SU treated group. Insulin sensitivity measured by homeostasis model assessment showed significantly greater improvement during pioglitazone treatment (Tan et al 2004a, b). In combination trials, pioglitazone produced significant additional improvement in glycemic control, as measured by FPG and HbA_{1c}. Secondary efficacy measures, including TG and HDL, also showed significant improvement after adding pioglitazone to SU (Kipnes et al 2001; Hanefeld et al 2004).

Improvement in HbA_{1c} was sustained throughout the double-blind phase and for 72 and 104 weeks in 2 open-label extension trials when combining pioglitazone with metformin or glibenclamide (Einhorn et al 2000; Tan et al 2004b).

Both pioglitazone and rosiglitazone are also approved for triple combination with metformin and a SU, producing significant additional decrease in HbA_{1c} and seem to be equally effective (Balfour and Plosker 1999; Gillies and Dunn 2000; Tran et al 2006).

In combination/comparative trials of pioglitazone and insulin, pioglitazone, when added to stable insulin regimens, significantly improved HbA_{1c} and FPG in patients with T2D. Pioglitazone treatment also provided significant benefit with respect to plasma HDL and TG levels and was as effective as a single injection of NPH at bedtime (Rosenstock et al 2002; Aljabri et al 2004; Mattoo et al 2005; Davidson et al 2006).

Side effects

During clinical trials, adverse events have been mild to moderate in severity with an overall frequency of adverse events being similar across the treatment groups (pioglitazone vs metformin, SU, or insulin). Adverse event profiles were different between treatment groups. During treatment with pioglitazone, edema and weight gain were reported more frequently, whereas gastrointestinal adverse events were reported more frequently in the metformin group. Hypoglycemia occurred at a higher incidence in patients treated with a SU or insulin (Aljabri et al 2004; Schernthaner et al 2004b; Charbonnel et al 2005; Belcher et al 2005; Jain et al 2006). There were no signs of hepatotoxicity in these studies. On the contrary there was a decrease in liver enzymes which also has been shown in other studies (Dorkhan et al 2006) and in the DREAM study with rosiglitazone (Gerstein et al 2006). Interestingly, several pilot trials have consistently shown positive effects of TZDs in the treatment of nonalcoholic steatohepatitis (NASH) (Caldwell et al 2001; Neuschwander-Tetri et al 2003; Sanyal et al 2004; Tiikkainen et al 2004) and Belfort et al reported recently in a placebo-controlled trial that administration of pioglitazone led to metabolic and histologic improvement in subjects with NASH (Belfort et al 2006). However, an increase in incidence of heart failure (Dormandy et al 2005) and bone loss in older women (Kahn et al 2006; Schwartz et al 2006) are the greatest matters of concern with TZDs at present, warranting further investigation.

Potential cardiovascular effects of pioglitazone HCL

As monotherapy or in combination with SU, metformin, or insulin, pioglitazone has shown consistent improvements in

TG and HDL levels with no significant effect on total or LDL cholesterol, the greatest degree of improvement occurring at the highest dosage in most cases. These changes ranged from about a 16% decrease in TG to a 12%–19% increase in HDL (Aronoff et al 2000; Rosenblatt et al 2001; Scherbaum and Goke 2002; Herz et al 2003). Treatment with pioglitazone seems to be associated with greater beneficial effects on blood lipid levels than treatment with rosiglitazone (Boyle et al 2002; Goldberg et al 2005). Pioglitazone also has shown to reduce dense LDL significantly and independently from fasting triglycerides and HDL cholesterol, suggesting the antiatherogenic potential of pioglitazone may be greater than that expected from its effects on triglycerides, LDL, and HDL cholesterol alone (Winkler et al 2003). In a study by Berhanu et al, there was marked improvements in lipid profiles in terms of LDL particle size and apolipoproteins after treatment conversion from rosiglitazone to pioglitazone in patients with T2D (Berhanu et al 2006).

There is some evidence on beneficial effect of TZDs on hypertension in patients with (Fullert et al 2002; Gerber et al 2003; Fukuen et al 2005; Derosa et al 2005a; IRIS 2007; Dormandy et al 2005) and without T2D (Fullert et al 2002).

TZDs have also been shown to increase adiponectin levels, which are reduced in obesity and negatively correlated to insulin resistance and development of arteriosclerosis (Forst et al 2005a; Pfutzner et al 2005a; Dorkhan et al 2006). However, the mechanism is not well understood yet but a recent study proposed that increased adiponectin production by pioglitazone was mediated through suppression of SOCS3 expression, playing an important role in improved insulin sensitivity (Kanatani et al 2007).

In other studies there have been evidences of reduction, regression or slowing progression of carotid intima media thickness (CIMT) (Nakamura et al 2004; Langenfeld et al 2005; Mazzone et al 2006) in patients with T2D when treated with pioglitazone as well as reduced neointimal tissue proliferation after coronary stent implantation and reduced in-stent restenosis (Takagi et al 2003; Marx et al 2005; Nishio et al 2006). The study by Mazzone et al was a randomized, double-blind, comparator-controlled, multicenter trial including 462 adults with T2D, comparing effect of pioglitazone vs glimepiride on CIMT during 18 months of treatment. The change in CIMT was less with pioglitazone vs glimepiride, and pioglitazone slowed progression of maximum CIMT compared with glimepiride similarly across prespecified subgroups based on age, sex, systolic blood pressure, duration of diabetes, body mass index, HbA_{1c} value, and statin use. In a pioneer study there was specific evidence of anti-inflammatory and antiatherogenic effect of pioglitazone versus glimepiride in terms of reduction in high-sensitiveity C-reactive protein, matrix metalloproteinase, and monocyte chemoattractant protein, independent of glycemic control (Pfutzner et al 2005b).

Data from several animal and human studies support the notion that TZDs even reduce urine albumin excretion and may prevent development of renal injury. There is, however, a relative lack of evidence demonstrating the effects of TZDs on hard renal outcomes as reviewed by Sarafidis and Bakris (2006) and there is need for studies with the particular objective of possible renoprotective effect of TZDs.

The PROspective pioglitAzone Clinical Trial In macro-Vascular Events (PROactive) study was the first randomized, double-blind outcome study in patients with T2D managed with diet and/or oral blood glucose-lowering drugs and/or insulin who had a history of macrovascular disease, assessing the effect of pioglitazone on the secondary prevention of macrovascular events. A total of 5238 patients were randomized with the cohort of patients, a typical type 2 diabetic population at high risk of further macrovascular events. The results were presented in 2005 after an average time of observation of 34.5 months. Treatment with pioglitazone reduced the secondary endpoint of combined all-cause mortality, non-fatal myocardial infarction, and stroke by 16% (Dormandy et al 2005), at the expense of increased heart failure (Yki-Jarvinen 2005). A recently published subgroup analysis from PROactive demonstrated that pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with T2D (Wilcox et al 2007).

Glimepiride in treatment of T2D

Effect on plasma glucose

Two systematic reviews on the effects and side effects of glimepiride (Campbell 1998; Inzucchi 2002) have been helpful in identifying randomized controlled trials (RCTs). Draeger et al (1996) found equivalent reductions in HbA_{1c} after 12 months' treatment with glimepiride (1–8 mg) or glibenclamide (2.5–20 mg) after titration to a common target. End mean HbA_{1c} in the glimepiride group was 8.4% and in the glibenclamide group 8.3%. The study was conducted in 1044 patients with T2D aged 26–81 years. All patients were previously treated with glibenclamide for ≥2 months; half the study population was thus transferred to treatment with glimepiride and half remained on glibenclamide. The purpose of the study was to show non-inferiority of glimepiride vs glibenclamide. Another RCT (Dills and Schneider 1996) studied 577 patients, mean age 59.5 years,

with type 2 diabetes previously treated with diet or any SU. No significant difference in HbA_{1c} was found at 52 weeks after treatment with glimepiride 1–12 mg or glibenclamide 1.25–15.00 mg titrated to pre-determined targets. HbA1c was reduced from 8.50 ± 1.20% (mean ± SD) at baseline to 8.24 ± 1.51% for glimepiride and from 8.50 ± 1.30% at baseline to 8.28 ± 1.48% for glibenclamide. Also in this study the main objective was to show non-inferiority of glimepiride compared with glibenclamide.

One study was found (Schernthaner et al 2004a) that compared adding modified release gliclazide (gliclazide MR) 30–120 mg or glimepiride 1–6 mg daily to current treatment (diet alone, metformin, or acarbose) in 845 patients with type 2 diabetes. It found no significant difference in HbA_{1c} at 27 weeks between gliclazide MR and glimepiride. HbA1c decreased similarly in both groups, from 8.4% to 7.2% on gliclazide MR and from 8.2% to 7.2% on glimepiride.

Several RCTs have been compared glimepiride with placebo as therapy added to lifestyle changes in drug-naive patients. In one such study (Luis Bautista et al 2003) glimepiride 1–4 mg (n = 48, mean age 48.4) or placebo (n = 22, mean age 50.7) was added to diet/exercise advice in Mexican Americans. Not surprisingly the HbA_{1c} reduction from baseline to end-point was statistically significant in favor of glimepiride after 14 weeks.

Side effects

Rosenstock et al (1996) reported no episodes of hypoglycemia (p-glucose <3.3 mmol/L) with either glimepiride 8–16 mg/day or placebo during a 14-week study in 416 patients previously treated with any drug in monotherapy. Luis Bautista et al (2003) found no significant difference in self-assessment of hypoglycemia reported over 14 weeks between patients taking glimepiride 1–4 mg or placebo and no confirmed episodes of hypoglycemia (plasma glucose <3.1 mmol/L). The weight gain was significantly higher in the glimepiride group compared with the placebo group.

Draeger et al (1996) found a lower incidence of hypoglycemia in people treated with glimepiride 1–8 mg compared with glibenclamide 2.5–20 mg. The incidence was 60 episodes with glimepiride and 74 episodes with glibenclamide. The effect on HbA_{1c} was the same in both groups, as reported above. The study by Dills and Schneider (1996) found a lower incidence of symptomatic hypoglycemia (12% and 17% respectively) in people treated with glimepiride 1–12 mg compared with glibenclamide 1.25–15.00 mg over 12 months.

Potential cardiovascular effects of SUs in general and glimepiride in particular

Initial concern for this issue was raised in the early 1970s when the University Group Diabetes Program assessed the efficacy of oral hypoglycemic treatment compared with insulin and diet alone in the prevention of cardiovascular complications. They demonstrated a significantly higher cardiovascular mortality in patients treated with SUs compared with diet alone (Prout 1971; Karam et al 1975). The United Kingdom Prospective Diabetes Study (UKPDS) attempted to answer the question of whether improved glycemic control reduced the risk of cardiovascular death in patients who were taking insulin or SUs (UKPDS 1998a, b). In that study no detrimental effect of SUs was noted, and the UKPDS is often cited as evidence that SUs do not increase cardiovascular risk to patients with type 2 diabetes. The UKPDS, however, did not ascertain the effect these agents had on patients with type 2 diabetes in the setting of acute coronary syndromes, ie, in patients directly at risk of myocardial infarction. The UKPDS patients were also newly diagnosed and known cardiovascular disease was an exclusion criterion; the absolute numbers of cardiovascular events were thus low. In a UKPDS substudy metformin in monotherapy was found to have a beneficial impact on cardiovascular events; this effect was not evident when SU was used in combination with metformin.

One review (Proks et al 2002) suggests that the SUR1 subunit of the KATP channel is mainly found in the beta-cell and that the SUR2 subunit of the KATP channel is found in smooth muscle and cardiac cells. It is further proposed that in humans, tolbutamide and gliclazide block channels containing SUR1 whereas glibenclamide, glimepiride, and repaglinide block both types of channels. It is, however, also clear that the inhibition of the KATP channel is not complete and that differences appear between drugs. In an extensive review (Quast et al 2004) the authors concluded that in animal models the coronary vasculature of several species respond to glibenclamide with vasoconstriction and a reduction of coronary blood flow and they also found indications in several studies that the vascular KATP channel plays a major role in the autoregulation of coronary blood flow in the animal and human heart in hypoxia. There has been a general lack of knowledge regarding the role of KAPT channels in the myocardium, the general belief being that the high ATP concentrations in the myocyte keep the KAPT channels closed under normal conditions. In one study, however (Zingman et al 2002), it was shown that in mice the knockout of Kir6.2 (the ion-conducting subunit of the KAPT channel) resulted in impaired cardiac performance during sympathetic

stimulation, pointing to a possible role of KAPT channels in maintaining cardiac cellular homeostasis not only in response to ischemia but also in the adaptive reaction to stress. The role of SUs in this context has not been studied.

Glimepiride binds predominantly to a 65 kDa subunit protein of the KATP complex while other SUs predominantely bind to a 140 kDa protein (Kramer et al 1994). The clinical relevance of these findings remains to be elucidated.

One study in perfused hearts in rats where coronary arteries were occluded by means of a snare (Mocanu et al 2001) showed that the beneficial effect of ischemic preconditioning was completely abolished by including glibenclamide in the perfusate but unaffected when including glimepiride. Other studies in animals (Geisen et al 1996) have also shown that glimepiride produced less cardiovascular effect than glibenclamide at equivalent blood glucose decrease in rats and dogs. In rabbit ventricular myocytes (Sato et al 2006), tolbutamide, gliclazide, and glimepiride had no effect on the mitochondrial KATP channel and did not affect the (cardioprotective) effects of the KATP-opener diazoxide. Glibenclamide on the other hand interfered with the effect of diazoxide and the authors concluded that glibenclamide interferes with the cellular pathways that confer cardioprotection whereas glimepiride, gliclazide, and tolbutamide do not.

Data from studies in humans are scarce, for obvious reasons. In one study (Ghosh et al 2001), tissue samples from the right atrium were obtained from patients of 7 different categories: non-diabetics, patients with type 2 diabetes both treated with KATP blockers and diet only, patients with type 1 diabetes, and patients with 3 different degrees of decreased ejection fraction (EF). Five protocols were used in a randomized fashion: 1. Control, incubation in oxygenated buffer; 2. Ischemia alone; 3. Preconditioning + ischemia; 4. Diazoxide + ischemia; 5. Glibenclamide + preconditioning + ischemia. Preconditioning was made by 5-min ischemia/5-min reoxygenation before a 90-min ischemia/120-min reoxygenation. Preconditioning prevented the effects of ischemia in all groups except patients with diabetes type 1 and 2 and those with the lowest EF. Diazoxide prevented effects of ischemia in all groups except patients with diabetes type 1 and 2. Glibenclamide abolished protection in non-diabetics and diet-controlled diabetes groups and did not affect diabetes type 1 and diabetes type 2 patients treated with KATP channel blockers.

One study in healthy male volunteers (Bijlstra et al 1996) showed that glibenclamide significantly inhibited the diazoxide-induced increase in forearm blood flow compared with placebo whereas glimepiride did not. The findings have been questioned in a later review (Riveline et al 2003).

There are a few important studies that try to study the role of glimepiride and ischemic preconditioning in real-life myocardial ischemia. In a double-blind RCT (Klepzig et al 1999), 45 predominantly male volunteers were divided into 3 groups when performing balloon angioplasty of high grade coronary artery stenosis. Each patient underwent 3 dilatations, and drugs were administered between dilatation 2 and 3. Balloon pressures and time intervals were identical in all 3 dilatations. Three drugs were infused intravenously in a randomized fashion: placebo, 1 mg glimepiride, or 2 mg glibenclamide. The primary variable was the mean ST segment shift during dilatation. Glimepiride and placebo groups showed a statistically significant reduction of mean ST segment shift between dilatation 2 and 3, interpreted as ischemic preconditioning. The glibenclamide group showed no difference in mean ST segment depression between dilatations. Direct comparison of the two drugs showed no statistically significant difference, as the power of the study was low.

One study from Taiwan (Lee and Chou 2003) investigated 20 patients with no diabetes and 23 patients with T2D when performing coronary angioplasty. The non-diabetic patients were given 10 mg glibenclamide (n = 6), 2 mg glimepiride (n = 7) or nothing (n = 7) before the angioplasty together with a glucose infusion to prevent hypoglycemia. No hypoglycemias were reported during the study. Patients with diabetes were taking either glimepiride (n = 12) or glibenclamide (n = 11). In both groups mean ST segment shift decreased between the first and the second balloon inflation in the control group and in the group taking glimepiride but not in the glibenclamide group. When nicorandil, an agent specifically activating mitochondrial KATP channels, was given i.v. to patients with diabetes before angioplasty there was no difference in mean ST segment shift in the glimepiride nor glibenclamide groups.

Combination of pioglitazone HCL and glimepiride in treatment of T2D

In vitro studies demonstrate that glimepiride has the potential to induce PPAR gamma activity, thereby improving insulin resistance (Fukuen et al 2005; Inukai et al 2005).

In a study of long-term effect of TZD on blood pressure in diabetic patients with metabolic syndrome treated with glimepiride there was significant improvement in systolic- and diastolic blood pressure after 12 months suggesting that the addition of a TZD to the glimepiride treatment of patients with

T2D and metabolic syndrome is associated with a significant improvement in the long-term blood pressure control, related to a reduction in insulin-resistance (Derosa et al 2005a). In a multicenter, randomized, double-blind, controlled clinical trial of treatment with pioglitazone or rosiglitazone added to glimepiride in patients with T2D and metabolic syndrome, 1 year of treatment with the pioglitazone combination was associated with significantly reduced plasma lipoprotein (a) levels, a known risk factor for cardiovascular disease, compared with the rosiglitazone combination (Derosa et al 2006).

Discussion

Diabetes is a strong, independent risk factor for cardiovascular disease, causing a 2- to 4-fold increase in cardiovascular mortality in patients with T2D (Panzram 1987; Stamler et al 1993; UKPDS 1998a, b; Stratton et al 2000). The two largest prospective diabetes studies, the UKPDS and the University Group Diabetes Program (UGDP) showed no statistically significant reduction of cardiovascular endpoints through improved glycemic control. Both pioglitazone and glimepiride are well tolerated and effective in achieving metabolic control in treatment of patients with T2D, as monotherapy or in combination. In spite of massive evidence of beneficial effects of pioglitazone on conventional and non-conventional cardiovascular risk factors, the results from the first prospective outcome study (Dormandy et al 2005) are still considered controversial and need confirmation. The latest Cochrane review on the subject has considered 22 RCTs including more than 6000 people treated with pioglitazone. They conclude that until new evidence becomes available, the benefit-risk ratio of pioglitazone remains unclear (Richter et al 2006).

There is no doubt that TZDs have contributed to our understanding of the pathophysiology of T2D and its treatment but there are still some unresolved issues about heart failure that require further study before a positive recommendation regarding their effects on cardiovascular risk reduction can be made. In our opinion, it is very important to estimate risk vs benefit in each individual in order to make appropriate therapeutic choices for patients with T2D.

Adequate circulating insulin is a prerequisite for TZD activity (Feinglos and Bethel 1998) and should be accounted for before initiating therapy, otherwise there is a risk that the full effect of TZDs cannot be achieved. For the practising physician it is of great interest to have instruments to identify individuals at risk of developing heart failure or to monitor cardiac function regularly during treatment. Natriuretic peptides can be candidates for both identifying individuals at risk to develop heart failure and to monitor the effect of TZDs on cardiac load, but there are for now no established recommendations addressing this issue (Jernberg et al 2004; Karthikeyan and Lip 2007). Some recent studies have been designed to identify factors associated with TZD effect (Phatak and Yin 2006; Wilcox et al 2007) but more studies are needed to help draw guidelines for individually adapted therapy choices as well as studies on markers of cardiovascular risk specifically. Several ongoing outcome studies are to be presented in the near future and these will undoubtedly increase our knowledge in this area. All evidence considered, it seems fair to conclude that the positive cardiovascular effects of TZDs (reduced hyperglycemia, improved dyslipidemia, decreased blood pressure, improved endothelial function, reduced central obesity, decreased inflammation, and decreased microalbuminuria) overweigh the negative ones (weight gain and increased heart failure).

The development of a new generation of TZDs, the partial PPARγ agonists with more specific action, may prove efficacious not only in treatment of T2D but also in prevention of atherosclerosis.

Glimepiride is a long-acting SU of recent origin. The glucose-lowering effects are well documented and comparable with those of other long-acting SUs. There is an ongoing controversy regarding SUs and other KAPT channel blockers and the risk of adverse effects on the heart. Since patients with diabetes have a greatly increased risk of developing and dying from cardiovascular disease, it would be appalling if it were proven that a remedy used for centuries in fact worsened the disease! Few would argue that, in the experimental setting, glimepiride can show effects on the heart and vessels that distinguishes it from its most common comparator, glibenclamide. The discussion has almost exclusively revolved around the phenomenon of ischemic preconditioning (IPC), described as a protective action taken by a heart subjected to a short ischemia and thus alleviating the effects of a longer ischemia. The different effects on the heart by the different KATP channel blockers result from their different affinity to SUR1 (mainly β-cell) and SUR2 (mainly heart and vessels) subunits of the SU (140K) receptor. The important question remains to be answered: do these differences matter in our drug-treated T2D patients? This question is clearly very difficult question to answer, since a prospective RCT is almost impossible to perform, but in a prospective study in France (Danchin et al 2005) 487 patients with acute myocardial infarction and diabetes were identified. Among the 215 patients with previous SU treatment, the in-hospital mortality was 10.2% compared with the non-SU (insulin, diet, other drugs) group mortality of 16.9% ($p = 0.035$).

The UKPDS remains our most important source of prospective data for risk vs treatment of T2D, and according to the UKPDS there is no obvious increase in cardiovascular risk when treating T2D with SUs.

On the other hand, it can be argued that if potential differences in the benefit of glimepiride can be detected in the experimental setting and treatments are comparable in other ways, we may let this influence our clinical decisions. As with the TZDs, we leave this to the discretion and clinical judgment of the reader.

Abbreviations

FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; HDL, high density lipoprotein cholesterol; OHA, oral hypoglycemic agents; PPARs, peroxisome-proliferator activated receptors; RCT, randomized controlled trials; SU, sulfonylurea; T2D, type 2 diabetes; TG, triglycerides; TZD, thiazolidinedione.

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